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(54) **Co-crystallization process**

(57) A process for isolating enantiomer components from a mixture of enantiomers through co-crystallization is disclosed, comprising the steps of (a) forming a solution comprising the mixture of enantiomers (R) and (S) and co-crystallization agents C₁ and C₂, wherein C₁ and C₂ are chiral or achiral, with the proviso that at least one of C₁ and C₂ is chiral and C₁ and C₂ do not form an enantiomeric pair, whereby C₁ forms a co-crystal with (R) and C₂ forms a co-crystal with (S); (b) super-saturating the solution in C₁ * (R) and C₂ * (S); (c) inducing crystallization of co-crystals of C₁ * (R) and C₂ * (S); and (d) isolating the C₁ * (R) co-crystals and C₂ * (S) co-crystals.

EP 1 034 826 A1

Description

Background of the Invention

[0001] The present invention relates to a process for isolating enantiomer components from a mixture of enantiomers, as well as to separating a racemate into its enantiomeric components. Separated, single enantiomers are extremely important in certain fields of use, since they contain desired properties whereas their enantiomer pair may contain undesirable properties.

[0002] Isolation of enantiomers from a mixture of enantiomers is typically difficult because the enantiomers generally have identical physical properties, such as melting and boiling points, or other such properties typically used for separation. Moreover they tend to crystallize as racemic crystals rather than as a conglomerate consisting of a mixture of pure enantiomer crystals which would be separable by preferential crystallization. Thus, a common way today to obtain enantiomers is not through isolating individual enantiomers from a mixture, but rather through asymmetric synthesis of the enantiomer.

[0003] Techniques for isolating enantiomers in use today include various embodiments of chromatography, such as simulated moving bed chromatography (SMB). Chromatography-based methods, however, to date are not capable of isolating some enantiomers and/or cannot isolate some enantiomers economically in commercial quantities.

[0004] Various crystallization methods have also been proposed for separating enantiomers from a mixture, including preferential crystallization, co-crystallization and emulsion-crystallization. C.f. EP 0 548 028 A1; WO 97/32644; EP 0 838 448 A1. While these methods overcome many of the shortcomings in crystallization, they also have some shortcomings. Preferential crystallization works only with racemates forming conglomerates. Furthermore, it is difficult to conduct with many conglomerates, since the systems tolerate only a small degree of super-saturation before spontaneous nucleation occurs.

[0005] In co-crystallization, the yields of the enantiomer to be isolated and its co-crystallization agent are often poor (< 95%), and it is normally difficult to recover the other enantiomer of the mixture in pure form. Furthermore, it can be difficult to identify a suitable co-crystallization agent that is inexpensive and readily accessible, and which enables crystallization of the desired enantiomer in high yield. Through emulsion crystallization some racemates forming racemic crystals can be separated, however the majority of the racemic crystals forming racemates cannot be separated even by normal emulsion crystallization.

[0006] It has now been found that the aforementioned problem can be avoided through the use of two co-crystallization agents which selectively form co-crystals with the (R) and (S) enantiomers of a mixture of

enantiomers. The co-crystals so-formed can then be readily isolated and subsequently treated to yield the desired enantiomers.

[0007] In another aspect of the invention, one or more enantiomers can be isolated from a mixture of enantiomers through co-crystallization from an emulsion. Use of an emulsion lends additional benefits characteristic of emulsion crystallization to the present invention.

Summary of the Invention

[0008] The present invention provides a process for isolating enantiomer components from a mixture of enantiomers through co-crystallization comprising the steps of (a) forming a solution comprising the mixture of enantiomers (R) and (S) and co-crystallization agents C_1 and C_2 , wherein C_1 and C_2 are chiral or achiral, with the proviso that at least one of C_1 and C_2 is chiral and C_1 and C_2 do not form an enantiomeric pair, whereby C_1 forms a co-crystal with (R) and C_2 forms a co-crystal with (S); (b) super-saturating the solution in $C_1 \cdot (R)$ and $C_2 \cdot (S)$; (c) inducing crystallization of co-crystals of $C_1 \cdot (R)$ and $C_2 \cdot (S)$; and (d) isolating the $C_1 \cdot (R)$ co-crystals and $C_2 \cdot (S)$ co-crystals.

[0009] A second aspect of the present invention provides a process for isolating one or more enantiomers from a mixture of enantiomers through co-crystallization from an emulsion comprising the steps of (a) forming an emulsion of organic liquid droplets in a continuous water phase, which emulsion contains the mixture of enantiomers and a co-crystallization agent for each enantiomer to be isolated, wherein the co-crystallization agents are chiral or achiral, with the proviso that at least one co-crystallization agent is chiral, whereby the co-crystallization agent forms a co-crystal with its corresponding enantiomer; (b) super-saturating the emulsion in (co-crystallization agent) \cdot (enantiomer); (c) inducing crystallization of co-crystals of (co-crystallization agent) \cdot (enantiomer), whereby crystallization takes place in the water phase; and (d) isolating the co-crystals of (co-crystallization agent) \cdot (enantiomer).

Detailed Description of the Invention

[0010] Crystallization processes are known and need not be described in detail here. Their basic premise is that a solution is formed containing the desired substance, the solution is super-saturated by conventional techniques such as cooling of the solution, and then crystallization of the desired substance is induced, either spontaneously or by seeding with seed crystals of the desired substance. The present extends this technology through the judicious choice of co-crystallization agents which will form co-crystals with the enantiomers of a mixture of enantiomers. The solution accordingly contains the enantiomers and the co-crystallization agents, is super-saturated, and then crystalli-

zation of co-crystals of the enantiomers and co-crystallization agents is induced.

[0011] Co-crystals of the co-crystallization agents and the enantiomers are indicated in the present invention according to the convention '(co-crystallization agent) * (enantiomer)'. In a typical embodiment of the invention, two co-crystallization agents, C_1 and C_2 , will be employed. They will, accordingly, selectively form co-crystals with the (R) and (S) enantiomers of the mixture of enantiomers, as indicated by ' C_1 * (R)' and ' C_2 * (S)'. All stoichiometries are intended to be covered with this nomenclature, i.e., ' C_1 * (R)' should be understood to include 1 C_1 * (R); 2 C_1 * (R); 1 C_1 * 2 (R); 2 C_1 * 3 (R); etc.

[0012] (R) and (S) may be present in the enantiomeric mixture in any ratio, including a 50/50 ratio, i.e. as a racemate. The mixture may comprise more than one pair of (R) and (S) enantiomers. The enantiomers can be bases in which case the co-crystallization agents typically will be acids. Or, the enantiomers can be acids in which case the co-crystallization agents typically will be bases. Bases will typically be amines. Alternatively, the enantiomers and/or co-crystallization agents can be neutral co-crystal-forming compounds.

[0013] The enantiomers can be pharmaceutical or agrochemical substances, fragrances, food additives, chemical intermediates or the like.

[0014] Co-crystallization agents are compounds that selectively form co-crystals with the (R) and (S) enantiomers. Co-crystallization agents may be either chiral or achiral, though at least one of them must be chiral. Preferably, both are chiral. Co-crystallization agents can not form an enantiomeric pair as this could lead to formation of a racemic co-crystal consisting of C_1 * C_2 * R * S.

[0015] An exception to the limitations on the co-crystallization agents applies to the case of co-crystallization from an emulsion (later described). In this case, the process of the present invention can be carried out using one co-crystallization agent to isolate a single enantiomer (R) or (S) from the mixture of enantiomers. The co-crystallization agent must be chiral. Where two co-crystallization agents are used to isolate both enantiomers, the co-crystallization agents can be chiral or achiral, with the proviso that at least one is chiral. In the case both are chiral they can form an enantiomeric pair. Typically, however, the conditions of the previous paragraph will also apply to emulsion crystallization.

[0016] The co-crystallization agents used in the present invention are preferably chosen according to the following guidelines:

- Co-crystals C_1 * (R) and C_2 * (S) should be less soluble than all other crystals that may form (e.g. C_1 * (R) * (S); (R) * (S); C_1 * C_2 * (R) * (S); etc), under the conditions at which crystallization takes place. In the case of emulsion crystallization, however, their solubilities can be somewhat higher than

those of other crystals, since control over what crystallizes is possible through seeding with the desired co-crystal (see also further discussion on emulsion crystallization);

- Concentrations of the co-crystallization agents and crystallization conditions are selected such that C_1 * (R) and C_2 * (S) can either be 1) alternately co-crystallized according to preferential crystallization: or, in the case of emulsion crystallization, 2) simultaneously crystallized, when differences in crystal size or shape between C_1 * (R) and C_2 * (S) allow separation by sieving or sedimentation;
- At least one of the co-crystallization agents is chiral.

[0017] In addition, C_1 and C_2 may each comprise a family of two or more co-crystallization agents. Each member of the family typically have a common base structure. The features defined above for C_1 and C_2 will apply to each member of the family.

[0018] Inducing crystallization (step (c)) can be carried out either by seeding with co-crystals of (co-crystallization agent) * (enantiomer) (i.e. C_1 * (R), C_2 * (S) etc.) or can occur without seeding (i.e. by spontaneous crystallization). Seeding can be consecutively; in the case of emulsion crystallization (see below) it can be carried out consecutively or simultaneously. In the case of consecutive seeding, the solution is first seeded with co-crystals of to induce crystallization of C_1 * (R) co-crystals, which co-crystals are then isolated from solution, and then the solution is seeded with co-crystals of C_2 * (S) to induce crystallization of C_2 * (S) co-crystals, which co-crystals are then isolated from solution. Or, this order of seeding can be reversed.

[0019] Prior to seeding, it is desirable that the super-saturated solution (or emulsion) contains no seed crystals of substances apart from those that are intended to be seeded. Any seeds present can be dissolved by ultrasound or heating, with such dissolving of seeds hereinafter referred to as "homogenisation".

[0020] Significant improvements in yields can be obtained if the crystallization process of the present invention is carried out with recycle of solution (or emulsion). This necessitates, in effect, that the solution (or emulsion) is replenished with the mixture of enantiomers and co-crystallization agents and then steps (a) - (d) are repeated. The order in which replenishing with the mixture of enantiomers and co-crystallization agents and steps (a) - (d) are repeated can vary. The mixture of enantiomers and co-crystallization agents can be replenished together, in a single step, following step (d). Or, the mixture of enantiomers and co-crystallization agents can be replenished after isolation of C_1 * (R) co-crystals and again after isolation of C_2 * (S) co-crystals. Other sequences are possible, as will be known to one skilled in the art.

[0021] By carrying out a recycle, several advantages are obtained. The co-crystallization agents, which are often costly, can be re-used. The process can be carried out continuously. Yield of co-crystal after each crystallization step need not be as high as is required in classical co-crystallization, whereas overall yield with recycle can be significantly higher. This enables the use of a variety of co-crystallization agents in the present invention, which in turn enables a wide range of mixtures of enantiomers to be resolved economically. Also, the present process isolates both enantiomers, whereas classical co-crystallization only one. The 'other' enantiomer can have value as an intermediate, as a co-crystallization agent for another separation process or to racemize it into the 'desired' enantiomer.

[0022] The desired enantiomer can be isolated from the co-crystallization agent using standard techniques, such as extraction of co-crystallizing acid by an alkaline solution or vice versa.

[0023] Particular advantages are gained if the crystallization is carried out from an emulsion. Emulsions allow, for example, crystallization at constant, low temperature with little or no spontaneous nucleation, extreme super-saturation, slow crystal growth, very regular crystal shapes, narrow distribution of crystal size and high purities.

[0024] Emulsions also allow the possibility of simultaneous seeding of co-crystals. Accordingly, the solution is seeded in step (c) simultaneously with seed co-crystals of $C_1 * (R)$ and $C_2 * (S)$, and the isolation of step (d) is carried out by separating co-crystals of $C_1 * (R)$ from co-crystals of $C_2 * (S)$ by sieving or sedimentation.

[0025] Emulsion crystallization can be used to isolate one or more enantiomers from the mixture of enantiomers.

[0026] Emulsions are, by definition, "droplets" dispersed in a "continuous phase". In the present invention, the droplets are organic liquid droplets and the continuous phase is a water phase. The emulsion optionally contains additives such as surfactants and dispersants, known in the art, for assisting formation and stabilization of the emulsion, and for facilitating the transport of the co-crystallization agent and/or enantiomer out of the organic liquid droplets and into the water phase, where crystallization takes place on a crystal surface (i.e. either the seed crystal or spontaneously formed crystal). Such surfactants and/or dispersants will be chosen according to the nature of the emulsion, and can be nonionic, anionic and/or cationic. The surface active agent will normally be present in an amount of 0.01-30 w/w %, preferably 0.1-20 w/w %.

[0027] The droplets typically vary in diameter from approximately 0.05 to 80 μm . Droplets with diameter in the range of 0.3 to 80 μm are known as "macrodroplets", and the emulsions as "macroemulsions". Droplets with diameter in the range of 0.05 to 0.3 μm are known as "microdroplets", and the emulsions as "microemul-

sions". For the sake of simplicity, the terms "droplets" and "emulsions" as used herein also encompass both macro- and microdroplets and macro- and microemulsions.

[0028] The organic liquid phase of the droplet will be water insoluble. 'Water insoluble' in this context means anything less than water miscible, though in most cases the organic liquid phase will mix with water in an amount not more than 30% w/w at the temperature at which crystallisation takes place.

[0029] In the emulsion of the present invention, at least one of the co-crystallization agents or enantiomers will be present primarily in the organic liquid droplets of the emulsion. 'Primarily' means in this sense its concentration in the organic liquid droplets is at least 20% higher than in the water phase.

[0030] The water may further contain a buffering agent, such as sodium acetate and acetic acid, for maintaining pH of the emulsion at a desired level, anti-freezing agents and solubility adjusting agents, as is known in the art.

[0031] Emulsions according to the invention can be formed using techniques known in the art. A suitable means of carrying out the invention is as follows:

Example 1 (consecutive seeding):

[0032] 10.0 g of (\pm)-Camphor-10-sulfonic acid (\pm -CSA), 8.45 g Brucine and 7.0 g Chinidine are dissolved in 43 ml microemulsion made from 10 % isobutanol, 30 % DMF, 20 % Synperonic NP 10 and 40 % water. Heating to approx. 95 - 100 °C and cooling leads to a clear microemulsion.

[0033] Preparation of the seeding crystals: 696.9 mg (+)-CSA and 1183.4 mg Brucine, and 696.9 mg (-)-CSA and 973.3 mg Chinidine are each dissolved in 5 ml of microemulsion made from isobutanol, Synperonic NP 10 and water, as described above. Crystallization takes place at room temperature over the course of several hours, yielding a suspension of co-crystals. The suspension is finely milled.

[0034] Seeding with the finely milled suspension of D-CSA * Brucine co-crystals results in crystal growth of D-CSA * Brucine co-crystals. After approximately thirty minutes the crystals are filtered off. In a second step the remaining microemulsion is homogenized and inoculated with a seed suspension of L-CSA * Chinidine co-crystals. After twenty minutes the precipitate of L-CSA * Chinidine is filtered off.

[0035] In order to recover the amines Brucine and Chinidine, a solution of NaOH in water (10 %) is added to the salts of D-CSA * Brucine or L-CSA * Chinidine and extracted twice with CH_2Cl_2 . The organic layer is dried over MgSO_4 and the solvent is evaporated under reduced pressure. The D- and L-CSA acids are recovered as the sodium salts in aqueous solutions.

Claims

1. A process for isolating enantiomer components from a mixture of enantiomers through co-crystallization comprising the steps of
 - (a) forming a solution comprising the mixture of enantiomers (R) and (S) and co-crystallization agents C_1 and C_2 , wherein C_1 and C_2 are chiral or achiral, with the proviso that at least one of C_1 and C_2 is chiral and C_1 and C_2 do not form an enantiomeric pair, whereby C_1 forms a co-crystal with (R) and C_2 forms a co-crystal with (S);
 - (b) super-saturating the solution in $C_1 \cdot (R)$ and $C_2 \cdot (S)$;
 - (c) inducing crystallization of co-crystals of $C_1 \cdot (R)$ and $C_2 \cdot (S)$; and
 - (d) isolating the $C_1 \cdot (R)$ co-crystals and $C_2 \cdot (S)$ co-crystals.
2. A process according to claim 1 wherein the mixture of enantiomers is a racemate of (R) and (S) enantiomers.
3. A process according to claim 1 or 2 wherein both the co-crystallization agents are chiral.
4. A process according to any one of the preceding claims further comprising replenishing the solution with the mixture of enantiomers and co-crystallization agents and repeating steps (a)-(d).
5. A process according to any one of the preceding claims wherein the enantiomers is a mixture are bases and the co-crystallization agents are acids, or the enantiomers are acids and the co-crystallization agents are bases.
6. A process according to claim 5 wherein the bases are amines.
7. A process according to any one of the preceding claims wherein crystallization is induced in step (c) by seeding with co-crystals of $C_1 \cdot (R)$ and $C_2 \cdot (S)$.
8. A process according to claim 7 in which the solution is first seeded with co-crystals of $C_1 \cdot (R)$ to induce crystallization of $C_1 \cdot (R)$ co-crystals, which co-crystals are then isolated from solution, and then the solution is seeded with co-crystals of $C_2 \cdot (S)$ to induce crystallization of $C_2 \cdot (S)$ co-crystals, which co-crystals are then isolated from solution, or this order of seeding is reversed.
9. A process according to any one of the previous claims wherein the solution is an emulsion of organic liquid droplets in a continuous water phase, and crystallization takes place in the water phase.
10. A process according to claim 9 in which $C_1 \cdot (R)$ and $C_2 \cdot (S)$ co-crystals are seeded simultaneously in step (c) and the isolation of step (d) is carried out by separating co-crystals of $C_1 \cdot (R)$ from co-crystals of $C_2 \cdot (S)$ by sieving or sedimentation.
11. A process according to any one of the previous claims further comprising isolating the enantiomer from the co-crystallization agent.
12. A process for isolating one or both enantiomers from a mixture of enantiomers through co-crystallization from an emulsion comprising the steps of
 - (a) forming an emulsion of organic liquid droplets in a continuous water phase, which emulsion contains the mixture of enantiomers and a co-crystallization agent for each enantiomer to be isolated, wherein the co-crystallization agents are chiral or achiral, with the proviso that at least one co-crystallization agent is chiral, whereby the co-crystallization agent forms a co-crystal with its corresponding enantiomer;
 - (b) super-saturating the emulsion in (co-crystallization agent) \cdot (enantiomer);
 - (c) inducing crystallization of co-crystals of (co-crystallization agent) \cdot (enantiomer), whereby crystallization takes place in the water phase; and
 - (d) isolating the co-crystals of (co-crystallization agent) \cdot (enantiomer).
13. The process of claim 12 wherein at least one of the co-crystallization agents or enantiomers is present primarily in the organic liquid droplets of the emulsion.
14. A process according to any one of the preceding claims wherein C_1 and C_2 each comprise a family of two or more co-crystallization agents.



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EUROPEAN SEARCH REPORT

Application Number
EP 99 20 0648

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|--|---|---|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.7) |
| A,D | EP 0 548 028 A (SANDOZ LTD) 23 June 1993 (1993-06-23) * claim 1; examples 1-3 * | 12 | B01D9/02 C07C209/88 |
| A,D | EP 0 838 448 A (DSM N.V.) 29 April 1998 (1998-04-29) * claims 1,3,11,15; example 1 * | 1,2 | |
| A | GB 865 311 A (AJINOMOTO CO.) * the whole document * | 1,2,8 | |
| A | JEAN JACQUES ET AL.: "Enantiomers, Racemates, and Resolutions" 1981, JOHN WILEY & SONS, NEW YORK XP002115263 * page 307 - page 317 * | 1,2,5,6 | |
| | | | TECHNICAL FIELDS SEARCHED (Int.Cl.7) |
| | | | B01D C07C |
| The present search report has been drawn up for all claims | | | |
| Place of search BERLIN | | Date of completion of the search 14 September 1999 | Examiner Bertram, H |
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**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 20 0648

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
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14-09-1999

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 548028 A | 23-06-1993 | JP 5293302 A | 09-11-1993 |
| | | US 5872259 A | 16-02-1999 |
| EP 838448 A | 29-04-1998 | NL 1004346 C | 24-04-1998 |
| | | CN 1182068 A | 20-05-1998 |
| | | JP 10245368 A | 14-09-1998 |
| | | NO 974779 A | 24-04-1998 |
| GB 865311 A | | NONE | |

EPO FORM P4458

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